Toxicity: Critical Variables

- Two variables are most important in determining the likelihood that exposure to a toxicant will result in an adverse response:
  - Amount of exposure (dose)
    - Should be distinguished from dosage, the amount relative to body weight, and absorbed dose (the amount actually in the body)
  - Frequency and duration of exposure (time)

Another Definition of Toxicity

- “The accumulation of injury over short or long periods of times that renders an organism incapable of functioning within the limits of adaptation or other forms of recovery.” (Rozman et al. 2001)
- This definition is organism centric, but environmental toxicology is necessarily focused on higher levels of organization
  - A lofty goal: protect the ecosystem

Policy Goal: No loss of fisheries from use of aquatic herbicide

<table>
<thead>
<tr>
<th>Assessment Endpoints</th>
<th>Indicators of Effects</th>
<th>Measurement Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of &gt;10% reduction in game fish production</td>
<td>Lab toxicity to fish</td>
<td>Fathead minnow LC50; larval bass concentration/mortality function</td>
</tr>
<tr>
<td>Lab toxicity to food-chain organisms</td>
<td>Daphnia LC50; Algal EC10</td>
<td></td>
</tr>
<tr>
<td>Field toxicity to fish</td>
<td>Caged fish bioassay (% mortality)</td>
<td></td>
</tr>
<tr>
<td>Population abundance in treated lake</td>
<td>Catch per unit effort; size/age ratios by age classes</td>
<td></td>
</tr>
</tbody>
</table>

Policy Goal: No unacceptable reductions in avian population

<table>
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<tr>
<td>Proportion of raptors killed within the region of use</td>
<td>Lab toxicity to prey</td>
<td>Rat LD50; Quail dietary LC50</td>
</tr>
<tr>
<td>Lab toxicity to raptors</td>
<td>Sparrow hawk dietary concentration/response function</td>
<td></td>
</tr>
<tr>
<td>Avian field toxicity</td>
<td>Number of prey carcasses per hectare; Number of dead or moribund raptors per ha</td>
<td></td>
</tr>
</tbody>
</table>

Policy Goal: No unacceptable reductions in avian population (cont’d.)

<table>
<thead>
<tr>
<th>Assessment Endpoints</th>
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<th>Measurement Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in rates of decline of declining bird populations in the region of use</td>
<td>Lab toxicity to birds</td>
<td>Quail dietary LC50; Starling dietary LC50</td>
</tr>
<tr>
<td>Avian field toxicity</td>
<td>Number of bird carcasses per hectare by species</td>
<td></td>
</tr>
<tr>
<td>Trends in population of declining birds</td>
<td>Rates of decline in areas of use as proportion of reference areas</td>
<td></td>
</tr>
</tbody>
</table>
Endpoints

- We are still stuck with measuring effects on individuals, even when we want to protect whole communities or ecosystems
- Must have endpoints if we are to measure toxicity at the individual level
  - An endpoint is the direct or indirect biochemical, cellular, physiological, or behavioral response following an exposure to a toxicant

Lethality Endpoint

- In the previous tables of policy goals and measurement endpoints, lethality as represented by the LD50 or LC50 was the most important endpoint on the individual level
  - LD50: dose lethal to 50% of the test population
  - LC50: concentration lethal to 50% of the test population

Other “Lower Level” Endpoints

- Biochemical
- Genetic
- Cellular
- Physiological
- Morphological
- Functional
- Behavioral

Testing Organisms (“The Guinea Pigs”)

- Mammalian toxicology for risk assessment
  - Rodents
  - Dogs
- Ecological toxicity testing for RA
  - Invertebrates, vertebrates, microbes, plants
  - Aquatic, terrestrial

Ecotox Testing: Aquatic Invertebrates

- *Daphnia magna* and other species
- Amphipod (scuds)
- Insects
  - Stoneflies
  - Mayflies
  - Midges

Ecotox Testing: Aquatic Vertebrates

- Coho salmon
- Atlantic salmon
- Fathead minnow
- Rainbow trout
- Bluegill sunfish
Ecotox Testing: Aquatic Plants

Green algae  Duckweed  Parrotfeather

Ecotox Testing: Terrestrial Invertebrates

Honey bee  Monarch butterfly

Ecotox Testing: Terrestrial Vertebrates

Mallard Duck  Northern Bobwhite Quail

Ecotox Testing: Terrestrial Vertebrates

Rat

Ecotox Testing: Terrestrial Plants

Corn  Wildflowers
Distribution of Individual Responses to Increasing Doses

50% Response (median)

Basis for Quantitatively Expressing Toxicity

Cumulative Proportion Responding

Basis for Quantitatively Expressing Toxicity

Probit Transformation-Linearization of the Dose-Response Curve

Utility of the LD50

Basis for Quantitatively Expressing Toxicity

Threshold

Hormesis

LD50; LC50

ED50; EC50

% Mortality

10  20  30  40  50  60  70  80  90

0.7  1.6  3.3  4.7  6.0  5.2  5.2  5.8  6.2

% Mortality as Probability Units

1  3  5  7

Log Dose

Threshold

- Expressed as the NOAEL or NOAEC
  - No Observable Adverse Effect Level
  - No Observable Adverse Effect Concentration
- In EPA risk assessments, empirically derived, although can be modeled based on curve fit function
- In rodent tests, based on chronic and subchronic exposure tests
- In ecotox tests, based on chronic exposure; i.e., life cycle tests

Hormesis

- "Low dose stimulation, high dose inhibition"
- Recent analysis of many studies shows it is a common phenomenon across species and compounds
Response of Five Algal Species to the Herbicide Diuron
(originally published by Ukeles 1962; reprinted in Calabrese & Baldwin 2002)

Factors Influencing Toxicity
- Factors related to toxic agent
- Factors related to exposure situation
- Factors related to the exposed organism
- Environmental factors related to the subject

Factors Influencing Toxicity

Factors related to toxic agent
Factors related to exposure situation
Factors related to the exposed organism
Environmental factors related to the subject

Route of Exposure

<table>
<thead>
<tr>
<th>Compound</th>
<th>Rat Oral LD50s (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>methoxyfenozide</td>
<td>1000</td>
</tr>
<tr>
<td>acetamiprid</td>
<td>100</td>
</tr>
<tr>
<td>carbaryl</td>
<td>10</td>
</tr>
<tr>
<td>phosmet</td>
<td>1</td>
</tr>
<tr>
<td>chlorpyrifos</td>
<td>1</td>
</tr>
<tr>
<td>azinphosmethyl</td>
<td>1</td>
</tr>
</tbody>
</table>

Driver et al. 1991, ETAC 10:21-33
Different Pathways of Bobwhite Exposure to Methyl Parathion
Oral LD50: 7.6 mg/kg
Dermal LD50: 9.2 mg/kg
NOAEC: 6.3 ppm (dietary)

Comparison of Hazard to Different Species

Effect of Bird Age on Toxicity

<table>
<thead>
<tr>
<th>Compound</th>
<th>LD50 (mg/kg)</th>
<th>LC50 (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDT</td>
<td>1</td>
<td>0.001</td>
</tr>
<tr>
<td>Diazinon</td>
<td>1</td>
<td>0.001</td>
</tr>
<tr>
<td>Permethrin</td>
<td>1</td>
<td>0.001</td>
</tr>
<tr>
<td>Thifensulfuron</td>
<td>1</td>
<td>0.001</td>
</tr>
<tr>
<td>Terbufos</td>
<td>700</td>
<td>600</td>
</tr>
<tr>
<td>Diazinon</td>
<td>700</td>
<td>600</td>
</tr>
</tbody>
</table>

Effect of Bird Age on Toxicity

<table>
<thead>
<tr>
<th>Age</th>
<th>DDT</th>
<th>Diazinon</th>
<th>Permethrin</th>
<th>Thifensulfuron</th>
<th>Terbufos</th>
<th>Diazinon LD50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>2</td>
<td>5</td>
<td>9</td>
<td>15</td>
<td>19</td>
<td>700</td>
</tr>
<tr>
<td>Adult</td>
<td>2</td>
<td>5</td>
<td>9</td>
<td>15</td>
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<td>15</td>
<td>19</td>
<td>700</td>
</tr>
</tbody>
</table>
Effect of Temperature & Infection
Chronic Toxicity of Pentachlorophenol to Clams
(Heinonen et al. 2001, ETAC 20(12):2778-84

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Exposure (µg/L)</th>
<th>Infection Status</th>
<th>Mean Survival Time (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 °C</td>
<td>100</td>
<td>Infected</td>
<td>611</td>
</tr>
<tr>
<td>5 °C</td>
<td>100</td>
<td>Uninfected</td>
<td>574</td>
</tr>
<tr>
<td>5 °C</td>
<td>300</td>
<td>Infected</td>
<td>525</td>
</tr>
<tr>
<td>5 °C</td>
<td>300</td>
<td>Uninfected</td>
<td>506</td>
</tr>
<tr>
<td>19 °C</td>
<td>100</td>
<td>Infected</td>
<td>136</td>
</tr>
<tr>
<td>19 °C</td>
<td>100</td>
<td>Uninfected</td>
<td>60</td>
</tr>
<tr>
<td>19 °C</td>
<td>300</td>
<td>Infected</td>
<td>63</td>
</tr>
<tr>
<td>19 °C</td>
<td>300</td>
<td>Uninfected</td>
<td>33</td>
</tr>
</tbody>
</table>

### Inverse Temperature Effects

- Generally, the higher the temperature, the greater the toxicity at a given concentration
- However, DDT and pyrethroid insecticides are exceptions
- Toxicity decreases with increased temperature and increases with decreased temperature